REMARKS:

Claims 1-12 and 14-18 are currently pending. Claims 12 and 14 are amended. The Examiner is reminded of the conditions for entering After Final amendments as set forth in 37 CFR 1.116. More specifically, 37 CFR 1.116 states in part:

> (a) An amendment after final action must comply with § 1.114 or this section.
> (b) After a final rejection or other final action (§ 1.113) in an application or in an ex parte reexamination filed under § 1.510, or an action closing prosecution (§ 1.949) in an inter partes reexamination filed under § 1.913, but before or on the same date of filing an appeal (§ 41.31 or § 41.61 of this title):
>
> > (1) An amendment may be made canceling claims or complying with any requirement of form expressly set forth in a previous Office action;
> > (2) An amendment presenting rejected claims in better form for consideration on appeal may be admitted; or
> > (3) An amendment touching the merits of the application or patent under reexamination may be admitted upon a showing of good and sufficient reasons why the amendment is necessary and was not earlier presented.

Applicants assert that their amendments clearly fit the guidelines as set forth above. Favorable action is requested.

General Comments Regarding Private PAIR

Applicants note that the Notice of Abandonment formerly placed in its private PAIR image file wrapper folder has been removed and thank the Examiner for correcting the issue.

Rejection under 35 USC §112 ¶2

Claim 12 is rejected for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Determining whether a claim is definite requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more. *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, (Fed. Cir. 1993).

The Examiner asserts that the terms "isolating resulting hydroxylated product from the medium" and "subterminally hydroxylated aliphatic carboxylic acids" are unclear. Applicants respectfully disagree.

The Examiner asserts that it is material whether or not terminally hydroxylated products are obtained. As Applicants explained in detail in their previous Office Action reply, the potential occurrence of by-products is completely irrelevant. Applicants have provided a method for hydroxylating an aliphatic C_8-C_{12}-carboxylic acid, which is novel and nonobvious over the prior art. The degree of purity of the obtained product is irrelevant as long as the instant claimed invention meets the requirements for patentability. The instant invention solves the technical problem of providing a process for production of subterminally hydroxylated carboxylic acids. No steps are omitted steps in the instant Claims.

The Examiner supports the stated opinion with two arguments:

a) "It is unclear how the enzymes are directed towards making only subterminally hydroxylated aliphatic carboxylic acids;" and

b) "it is not clear how subterminally hydroxylated carboxylic acids are separated from terminally hydroxylated carboxylic acids?

In regards to argument a) - there is no requirement in the MPEP, by the Federal Circuit or otherwise to demand such a high degree of enzyme specificity. The inventive concept is a process for producing subterminally hydroxylated carboxylic acids and said process is a novel and unobvious process invented the Applicants. The limitations required by the Examiner (production of only subterminally hydroxylated carboxylic acids) are unnecessary and highly artificial. Applicants direct the Examiner to section 101 of title 35, United States Code, which provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Further, the Examiner is directed to MPEP 2106 (V)(A)(1) which provides in part:

> The invention set forth in the claims is presumed to be that which applicant regards as the invention

Applicants respectfully submit that the Claims, as recited, set forth that which Applicants regard as their invention and that said invention is new and useful. Applicants Claims recite a process for the enzymatic production of subterminally hydroxylated aliphatic carboxylic acids and as such, only said recitation of hydroxylated aliphatic carboxylic acids should be analyzed for patentability, not the byproducts of said reaction. In this regard, Applicants wonder why the

Examiner is continually requesting arguments regarding unclaimed recitations and unclaimed subject matter completely unrelated to the patentable subject matter as presented by the Applicants in their application.

Assuming *arguendo* that terminally hydroxylated aliphatic carboxylic acids should be addressed when determining the patentability of a process that produces subterminally hydroxylated aliphatic carboxylic acids, as far as argument b) is concerned, it would be trivial to purify a product mixture if subterminally hydroxylated carboxylic acids of higher purity are desired. It must be noted to the Examiner that the skilled artisan who might want to practice the instant invention would have at least some rudimentary chemical knowledge. Methods for isolating reaction products and, if necessary, separating individual compounds from complex mixtures of reaction products are truly considered basic chemical skills which are taught to first-year students of chemistry. Moreover, as indicated in Applicants previously submitted response, the instant Specification provides guidance for such a separation: Method 6 of the instant Specification discloses chromatographic methods. Consequently, it would have been of little effort for one of ordinary skill in the art to further modify chromatographic separation methods if necessary.

Claim 14 is rejected as being indefinite for allegedly failing to point out and distinctly claim the subject matter which the Applicants regards as the invention. The Examiner asserts that it is unclear if the amino acid substitutions are in the alternative or are all inclusive. While neither agreeing with the Examiner's reasons for said objection nor with said rejection's correctness, Applicants have amended the Claims referred to by the Examiner in order for a more timely prosecution of the instant application.

Claims 12, 14 and 16-18 are rejected as being indefinite for allegedly failing to point out and distinctly claim the subject matter which the Applicants regards as the invention. The Examiner asserts the metes and bounds of the term "is derived from Bacillus megaterium" are unclear. Applicants respectfully disagree. While the Examiner provides a number of entertaining dictionary variations on possible meanings of said term, Applicants urge that one of ordinary skill in the art, the practitioner against whom all §112 ¶2 rejections for indefiniteness are based, would readily understand the meaning of said term in the context of the instant application. The Examiner is reminded it is well settled that the "language of the claims, read in light of the specification" is to be considered when determining whether the Claims are definite.

(*Allen Archery Inc. v Browning MFG. Co.*, 819 F.2d 1087, 1092 (Fed. Cir. 1987)). This precept has been incorporated into the MPEP which states that "[t]he meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification with clear disclosure as to its import." (MPEP §608.01(o). *See also* 37 CFR 1.75 (c) wherein it states in part that "the meaning of the terms in the claims may be ascertainable by reference to the description.")

Moreover, the definiteness of the language employed "must be analyzed - not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one processing ordinary skill in the pertinent art." (*In re Angstadt*, 537 F.2d 498, 501 (C.C.P.A. 1976)(quoting *In re Moore*, 439 F.2d 1232,1235 (C.C.P.A. 1971)). The law is clear that "if the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is a precise as the subject matter permits, the courts can demand no more." (*North Am. Vaccine, Inc. v American Cyanamid Co.*, 7 F.3d 1571, 1579-1580 (Fed. Cir. 1993)).

Further, Applicants direct the Examiner to the paragraph bridging pages 2 and 3 of the instant Specification, wherein Applicants define the meaning of said term by explaining what is done when a monooxygenase is **derived** from *B. megaterium*.

Accordingly, Applicants assert the metes and bounds of the term "is derived from Bacillus megaterium" are clear to one of ordinary skill in the art when said claim term is read in light of the instant Specification.

Claims 12, 14 and 16-18 are rejected as being indefinite for allegedly failing to point out and distinctly claim the subject matter which the Applicants regards as the invention. The Examiner asserts that the metes and bounds of the terms "in accordance with SEQ ID NO:2" and "according to SEQ ID NO:2" are unclear. While neither agreeing with the Examiner's reasons for said objection nor with said rejection's correctness, Applicants have amended the Claims referred to by the Examiner in order for a more timely prosecution of the instant application.

Claims 12, 14 and 16-18 are rejected as being indefinite for allegedly failing to point out and distinctly claim the subject matter which the Applicants regards as the invention. The Examiner asserts the metes and bounds of the term "functional mutation" are unclear. Applicants respectfully disagree. As discussed above, Claims must be analyzed in light of the Specification. The Examiner is directed to page 3, lines 13-17 of the instant Specification for a

reading of the term "functional mutation."

Accordingly, since Applicants urge that all of the Examiner's rejection under 35 USC §112 ¶2 have been addressed and overcome, Applicants respectfully request withdrawal of said rejections. Favorable action is solicited.

Rejection under 35 USC §112 ¶1

Claims 12, 14 and 16-18 are rejected for allegedly failing to convey to one skilled in that that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree.

In regards to all the 112 ¶1 rejections, it must be remembered that to satisfy the written description prong of 35 USC §112 ¶1, the Specification must only describe the invention in sufficient detail so that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). No particular form of disclosure is required, but "the description must clearly allow persons of ordinary skill in the art to recognize that [the patentee] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989) (citing *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976)).

The Examiner believes that the limitation that a derivative of C_8-C_{12}-carboxylic acids be selected from an alkyl ester, an amide or an anhydride thereof and the limitation that if the mutant enzyme comprises F87A, said mutant must comprise another mutation is not described in the instant Specification as filed. Applicants respectfully disagree.

The Examiner is directed to part a1) of Claim 12, as originally filed, wherein said Claim recites a recombinant microorganism as claimed in Claim 10 or 11. Claim 10 in turn refers to a vector according to Claim 9, comprising an expression construct according to Claim 8, which encodes a nucleic acid sequence as claimed in Claim 7. Said nucleic acid encodes a monooxygenase as claimed in any of the preceding claims, and consequently, encodes a monooxygenase according to Claim 3. Claim 3 recites the aforementioned rejected limitation. Further, part a2) of Claim 12, as originally filed, directly refers to a monooxygenase of any of Claims 1 to 6, and as such, also to a monooxygenase according to Claim 3.

Further, The Examiner is directed to the instant Specification, page 10, lines 33-38, wherein C_8-C_{12}-carboxylic acids and their derivatives are disclosed as especially preferred

embodiments of the instant invention. The skilled artisan is of course well aware of alkyl esters, amides and anhydrides as potential derivatives, especially since said derivatives, in addition to being known in the art, have been disclosed on page 2, lines 35-36 of the instant Specification.

Accordingly, the instant Application, as filed, supports the rejected Claims. Favorable action is solicited.

The Claims are written in such a manner that the problems of insufficient numbers of examples as described by the Examiner in the Office Action should not apply. Applicants' invention is not drawn to any or all P450 monooxygenases instead, said invention relates to a process for the enzymatic production of subterminally hydroxylated aliphatic carboxylic acids and as such, is adequately described in the instant application. The MPEP states that a "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces" and as such, a single species may be enough to identify the entire genus (*see* MPEP 2163.II.A.3.a.ii.). A recent Federal Circuit case supports the statements of the MPEP. When discussing what is required for a written description the court said "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution" (*Capon v. Eshhar*, 418 F.3d 1349, 1358; 2005). Further, in overturning a BPAI decision, which relied on similar rejections reasons as stated in the instant Office Action, where both parties to an interference had all Claims in their respective patents cancelled for failing to meet the written description requirement, the court stated that "[t]he Board erred in refusing to consider the state of the art of the scientific knowledge" and when citing *Lilly* and *Fiers* spoke of a rulings in view of a "wish" list provided in said inventions, and not the state of the relevant art (*Id.* at 1357). Further, the court stated, that "[i]t is not necessary that every permutation with a generally operable invention be effective in order for an inventor to obtain a generic claim" and both parties were lauded because they "present[ed] not only general teachings... but also specific examples" (*Id.* at 1359).

Applicants assert that the instant Specification fully complies with all the aforementioned requirements because it allows one of ordinary skill in the art to practice the instant invention. Applicants provide in the instant Specification summary information such as the function of cytochrome P450 monooxygenase and general molecular biology techniques which meet the

"general teachings" prong. Further, Applicants have supplied "specific examples" of the instant invention as required of the second prong of *Capon*. As listed by the Examiner on page 8 of the instant Action, the instant Specification teaches a method for hydroxylating 15-pNCA, 12-pNCA, 10-pNCA or 8-pNCA with a modified P405 monooxygenases of SEQ ID NO:2 having mutations at residue 26, 47, 74, 87, 188 or 354. Thus while not required to provide even a single working example (*See, In re Gosteli* above - no specific form of the disclosure is required), Applicants have provided such examples as set forth above, as listed by the Examiner in the instant Office Action, and in the instant Specification.

Further still, while the monooxygenase domain of P450 BM-3 encompasses over 400 amino acids and techniques for large scale screening are available, Applicants have described the regions to be modified in order to obtain functional mutations and have thusly provided the guidelines for a highly directed exercise.

Moreover, according to accepted principles of patent practice Applicants are not merely entitled to the literally disclosed invention. If that were the case then the scope of protection would be limited to the disclosed examples. However, Applicants are rather entitled to the whole range of embodiments which is made accessible by their invention and which is properly claimed therein. In the instant application, Applicants have disclosed a sequence to be taken as the basis for mutations (SEQ ID NO:2) as well as selected regions to mutated in order to obtain a desired effect. The examples (*See*, in particular, Table 4) demonstrate that said effect has been achieved. Consequently, the instant invention has been sufficiently disclosed, sufficiently supported by experimental data and thus, provides sufficient written description for the entire genus based on the applicable standards. Therefore, Applicants respectfully urge that the Examiner has mistakenly applied a too strict an interpretation for claiming a genus and that Applicants are entitled to claim additional embodiments which are not represented by individual examples, i.e. the genus form the species recited.

Accordingly, for at least the reasons described above, the instant Application does provide an adequate written description for one of ordinary skill in the art to practice the instant invention and withdrawal of the instant rejections is respectfully requested. The instant Specification in combination with what would have been known by a skilled artisan at the time of filing, provides sufficient written description support to clearly conclude that the inventor "at the time the application was filed, had possession of the claimed invention." Favorable action is

solicited.

Regarding the enablement requirement of §112, the Federal Circuit has held that "[t]he specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they a ready know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation'." (*Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. (2003)). The Claims, as currently amended, are fully enabled by the Specification of the instant application in combination with the general knowledge of one of ordinary skill in the art.

The Examiner recites the standard USPTO phraseology in rejecting the instant Claims. Applicants assert that said phraseology is inappropriate for the instant application. The Examiner alleges, for example, that the instant disclosure presents no guidance or working examples of the use of any or all mutants, recombinants, or variants of any or all cytochrome P450 monooxygenase. Applicants direct the Examiner to the instant Claims where it is recited that said invention relates to a nucleic acid sequence encoding a monooxygenase which is derived from *Bacillus megaterium* cytochrome P450 monooxygenase BM-3 with an amino acid sequence of SEQ ID NO:2 which has a functional mutation in the amino acid sequence region 86-88. The Claims, contrary to the Examiner's assertions and the USPTO biotechnology standard rejection terminology, encompass merely what is recited in the instant Claims with enough examples for one of ordinary skill to practice the instant invention without undue experimentation. As stated above, the instant Specification provides a number of working examples for the skilled artisan to use as a basis for said practice of the instant invention. Additionally, as described in *Capon*, as the skill in the art progresses so to does the analysis of the inventions in said art. Applying *Capon* and the relative state of the art at the time of filing, one of ordinary skill would be able to create the working examples the Examiner asserts are lacking.

Further, Applicants have provided the specific mutations listings of specific mutations of the instant invention. In instant Claims 14 and 18, the Applicants have indicated specific individual amino acid mutations. In at least said Claims, one of ordinary skill would clearly be enabled to practice the instant invention based on the discourse of the instant application. Thus, Applicants respectfully urge that the instant Specification is sufficiently clear that one of ordinary skill in the art would be provided enough information in the disclosure for one of

ordinary skill in the art to practice the invention.

Further still, the Examiner asserts that the specific amino acid positions within a given protein sequence that can be modified is unpredictable and that one of skill in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification. Applicants respectfully disagree. Based on what is actually claimed in the instant application, not the "claimed mutants and variants of any cytochrome P450 monooxygenase" as asserted by the Examiner, the computational techniques available at the time of filing for protein structural predictions based on sequence listings. (*See e.g.*, The Boston University Protein Sequence Analysis server available at http://bmerc-www.bu.edu/psa/) and what was known in the art, modification of the instant claimed sequence would have been routine to one of ordinary skill in the art.

Applicants respectfully assert that the instant Claims are enabled based upon the requirements of §112, the MPEP and the rulings handed down from the Federal Circuit. One of ordinary skill in the art would have been able to practice the instant invention without undue experimentation based on a combination of the contents of the instant Specification when analyzed by the skill in the art at the time of filing. Accordingly, Applicants respectfully request withdrawal of the instant enablement rejections and favorable action is solicited.

Rejection under 35 USC §102

Claims 12, 14 and 16-18 are rejected for allegedly being anticipated by Graham-Lorence et al. Applicants respectfully disagree.

Anticipation can only be established by a single prior art reference which discloses each and every element of the claimed invention. *RCA Corp. v. Applied Digital Data Systems, Inc.*, 730 F.2d 1440, 1444, 221 USPQ 385, 388 (Fed. Cir. 1984). The identical invention must be shown in as complete detail as it is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). It is not enough, however, that the reference discloses all the claimed elements in isolation. Rather, as stated by the Federal Circuit, the cited art reference must disclose each element of the claimed invention "arranged as in the claim." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983).

Applicants Claims recite at least one hydroxylatable C_8-C_{12}-carboxylic acid or a derivative thereof – nowhere is an arachadonic acid recited. One of ordinary skill in the art

would never mistake a C_8-C_{12}-carboxylic acid or a derivative thereof for a 20 carbon fatty acid. As discussed above, the Claims must be read in light of the Specification, they must not be read in a vacuum. Applicants respectfully urge that reading the term C_8-C_{12}-carboxylic acid or a derivative thereof to read on a 20 carbon fatty acid is reading said Claim recitation in a vacuum and devoid of the disclosure of the instant Specification. As a result, the cited art fails to teach an element, a C_8-C_{12}-carboxylic acid or a derivative thereof, of instant Claim 12 and as such fails to anticipate said Claim.

Further, assuming *aguendo* that the term "selected from an alkyl ester, an amide or an anhydride thereof" is unclear, the proper placement of such a statement is in a §112 ¶2 rejection[1]. Since the Examiner has not rejected the aforementioned term under 35 USC §112 ¶2, Applicants respectfully submit that said term is clear and one of ordinary skill in the art would have known, at the time of filing, that the cited art fails to teach or disclose a C_8-C_{12}-carboxylic acid or a derivative thereof selected from an alkyl ester, an amide or an anhydride. Accordingly, the instant Claims do not read on the 20 carbon fatty acid of the cited art.

For at least the arguments listed above, Graham-Lorence et al. fails to teach each and every element of the instant Claims as arranged in said Claims. Since the cited art does not teach each and every element of the Claims, it does not anticipate the Claims. Applicants therefore respectfully request withdrawal of the rejection under 35 USC § 102(b). Favorable action is solicited.

[1] A rejection under §112 ¶2 for the term "selected from an alkyl ester, an amide or an anhydride thereof" would be new grounds for rejection and would require the withdrawal of the Final status of the instant Action.